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Highlights

- A literature review dealing with medical treatment of vascular prosthesis infections was performed.
- The microbiological epidemiology of vascular prosthesis infections was highlighted.
- Indications and modalities of empirical antibiotherapy are proposed.
- Documented antibiotherapy of vascular prosthesis infections is described.

Medical treatment of prosthetic vascular graft infections: review of the literature and proposals of a Working Group

M. Revest ^{a,b}, F. Camou ^c, E. Senneville ^d, J. Caillon ^e, F. Laurent ^f, B. Calvet ^g, P. Feugier ^h, M. Batt ⁱ, C. Chidiac ^{j,*}; Groupe de Réflexion sur les Infections de Prothèses vasculaires (GRIP)

^a *Infectious Diseases and Intensive Care Unit, Pontchaillou University Hospital, Rennes, France*

^b *CIC Inserm 1414, Rennes 1 University, Rennes, France*

^c *Intensive Care Unit, Saint-André University Hospital, Bordeaux, France*

^d *Infectious Diseases Department, Gustave Dron Hospital, Tourcoing, Lille 2 University, France*

^e *Bacteriology Department, EA 3826 Nantes University, Hôtel Dieu University Hospital, Nantes, France*

^f *Bacteriology Department, International Center for Infectiology Research (CIRI)–INSERM U1111, CNRS UMR5308, Lyon 1 University, ENS de Lyon, Hospices Civils de Lyon, Lyon, France*

^g *Anesthesiology Department, Beziers, France*

^h *Department of Vascular Surgery, University Claude Bernard Lyon 1, Hospices Civils de Lyon, Lyon, France*

ⁱ *Department of Vascular Surgery, University of Nice-Sophia Antipolis, Nice, France*

^j *Infectious Diseases Department, University Claude Bernard Lyon 1, Hospices Civils de Lyon, Inserm U1111, Lyon 1 University, Lyon, France*

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* Corresponding author. Present address: Infectious Diseases Department,
University Hospital of Lyon, Inserm U1111, University of Lyon 1, Hôpital de la Croix
Rousse, 103 Grande rue de la Croix Rousse, 69004 Lyon, France. Tel.: +33 4 72 07
11 07; fax: + 33 4 72 07 17 50.

E-mail address: christian.chidiac@chu-lyon.fr (C. Chidiac).

ABSTRACT

More than 400 000 vascular grafts are inserted annually in the USA. Graft insertion is complicated by infection in 0.5–4% of cases. Vascular graft infections (VGIs) are becoming one of the most frequent prosthesis-related infections and are associated with considerable mortality, ranging from 10–25% within 30 days following the diagnosis. Treatment of VGI is based on urgent surgical removal of the infected graft followed by prolonged antibiotherapy. Data regarding the best antibiotherapy to use are lacking since no well designed trial to study antimicrobial treatment of VGI exists. Moreover, since VGIs demonstrate very specific pathophysiology, guidelines on other material-related infections or infective endocarditis treatment cannot be entirely applied to VGI. A French multidisciplinary group gathering infectious diseases specialists, anaesthesiologists, intensivists, microbiologists, radiologists and vascular surgeons was created to review the literature dealing with VGI and to make some proposals regarding empirical and documented antibiotic therapy for these infections. This article reveals these proposals.

1. Introduction

Due to advances in surgical techniques and increased possibilities for interventional radiology, the number of patients with vascular implants is constantly on the rise [1]. Prosthetic vascular graft infections (PVGIs) are among the most serious complications associated with these procedures. Their frequency, ranging from 1–5% of patients, varies depending on the anatomical implantation site, the biomaterial used and the patient's co-morbidities. The mortality rate is estimated to be 10–25% within 30 days after the diagnosis and almost 50% after 1 year, and the risk of amputation is estimated at 4–14% [2]. However, there are very few validated data on the best medical treatments for these infections. A focus group composed of French vascular surgeons, anaesthesiologists, microbiologists, intensivists, radiologists and infectious diseases specialists was conducted to review the literature on the subject and to formulate proposals for anti-infective therapies for PVGIs.

2. Methodology

This study relates to aortic (chest and abdominal) and peripheral PVGIs, including prosthetic arteriovenous fistula infections and axillofemoral bypass graft infections. Venous or arterial catheter infections, endovascular stimulation material infections and autologous graft infections were excluded.

A French and English literature search was conducted through PubMed for the period 1 January 1991 to 1 March 2013 using a selection of keywords from the

Medical Subject Heading (MeSH) database as well as other unreferenced keywords. From the 9188 references thus selected, the following were excluded: series with less than 10 cases; in vitro studies; and incomplete or insufficiently documented series. Some animal studies were retained for the analysis when they were considered to be sufficiently informative. Series on arteriovenous fistula infections carried out on bovine carotid grafts were also excluded. The bibliographic references for all publications selected were reviewed. All of the studies that were retained were reviewed using the grid proposed by the Society for Vascular Surgery [3]. The recommendations are graded in accordance with the Haute Autorité de Santé (French Health Authority) methodology sheet from December 2010 (Table 1) [4]. In the absence of data, they correspond to recommendations based on a professional consensus (expert opinion) within the Working Group. Forty-six clinical studies were thus selected for analysis [5–50]. There were 43 cohort studies, with the number of patients ranging from 11 [8,19,21] to 187 [32] (mean, 49; median, 32) and a case–control study involving 51 cases, for a total of 102 controls [34]. Four animal studies were also retained for analysis [51–54].

3. Empirical antibiotic therapy

3.1. Rationale

3.1.1. Microbiological information

The microbiological epidemiology of PVGIs is broken down as follows:

Staphylococcus aureus, 20–53%; Enterobacteriaceae, 14–41%; coagulase-negative staphylococci (CoNS), 15%; *Pseudomonas aeruginosa*, *Streptococcus* sp. and

Enterococcus sp., 10–15%; polymicrobial infection, 20%; obligate anaerobic bacteria (always associated with other bacteria), 5%; and yeast, 1–2%.

3.1.2. Indication

In the study by Legout et al. [33], the proportion of intra-operative samples with positive culture did not differ between patients who did or did not receive antibiotics before revision surgery, i.e. 38/43 vs. 40/42, respectively ($P = 0.4$). However, patients who received antibiotherapy prior to surgery were operated within the first 48 h of treatment, and these results do not rule out the possible loss of microbiological information for patients treated >48 h prior to surgery, nor do they allow for the recommendation of empirical antibiotic therapy for all PVGI situations.

The issue of non-prescriptive empirical antibiotic therapy arises only when the patient has not received antibiotics prior to admission and when the expected time between diagnosis or suspicion and the revision surgery is short. No data are available to define the acceptable length of the expected timeframe for revision surgery beyond which empirical antibiotic therapy should be initiated. Ideally, this should be decided on a case-by-case basis as part of a multidisciplinary consultation.

3.1.3. Choice of antibiotics

3.1.3.1. Impact of the biofilm

Biofilm developed on the vascular prosthesis plays a particular role in the difficulties encountered in treating PVGIs. Biofilm is formed by surface-associated communities

of micro-organisms embedded in an extracellular matrix that acts as both a barrier against antibiotic penetration and protection against host defences [55]. Moreover, bacteria express a distinct metabolic pathway within the biofilm [56]. Whilst planktonic bacteria found outside the biofilm or in the very top layers of it display active metabolism and are therefore fully sensitive to antibiotics that mainly impair bacterial mechanisms of replication, bacteria embedded deeply in a mature biofilm demonstrate very slowed-down metabolic pathways and a decreased efficacy of antibiotics [56,57]. In this context, curing PVGIs with antibiotics alone without removal of the infected device therefore seems elusive.

There are very few data, if any, regarding the efficacy of antibiotics on infected vascular graft biofilm. An in vitro study evaluated the impact of various antimicrobial agents on staphylococcal adherence on Dacron® or polytetrafluoroethylene (PTFE). In this model, daptomycin and rifampicin were the two best agents to eradicate staphylococcal biofilm, whereas vancomycin and ceftriaxone failed to sterilise it [58]. Other authors investigated the capabilities of various antibiotics to penetrate biofilm formed on other medical devices. Rifampicin is probably the antimicrobial agent that demonstrated the best activity on staphylococcal biofilm [54,59–63]. When in combination, fosfomycin has been found to enhance the antimicrobial activities of many antibiotics in methicillin-resistant *S. aureus* (MRSA) biofilm [64]. Daptomycin has also demonstrated interesting capacities in biofilm penetration [65], and some studies revealed a higher activity against stationary phase staphylococci than vancomycin [66]. However, the clinical relevance of all these in vitro data is still lacking and the therapeutic choice of the antimicrobial chemotherapy to use to treat

PVGIs cannot be only based on such biofilm penetration criteria, highlighting that clinical studies and data are required.

3.1.3.2. Gram-positive cocci

The prevalence of MRSA has steadily declined in Europe since 2001 but remains >20%. The situation is different for CoNS, with resistance to β -lactams [67], glycopeptides (including teicoplanin) [68] and, more recently, linezolid [69] steadily on the rise.

The risk factors associated with methicillin-resistant staphylococci (MRS) (*S. aureus* or CoNS) in PVGI were examined in a retrospective study [41], which determined that the proportion of PVGIs caused by MRSA was 16%. The only factor identified was the existence of hypertension, but this relationship could not be explained.

Given the important role of staphylococci in PVGIs, the significant proportion of MRSA and the absence of clinical risk factors validated by the methicillin resistance, it is recommended that the spectrum of empirical antibiotic therapy for PVGIs should systematically cover MRSA.

Anti-Gram-positive antibiotics used in empirical antibiotic therapy for PVGIs should ideally be bactericidal against bacteria both in the stationary growth phase and when growing exponentially, and they should have a spectrum that covers MRS [including strains whose glycopeptide minimum inhibitory concentrations (MICs) are ≥ 1.5 mg/L], good tissue distribution (including biofilm), an anti-adhesion effect and a good safety profile (including a kidney safety profile) that is compatible with the characteristics of patients with PVGIs. Considering these elements, linezolid and

tigecycline are less than ideal due to their solely bacteriostatic action and their failure to demonstrate their benefits in bacteraemic patients and/or in patients with severe infection; the same applies for teicoplanin [67], the anti-CoNS spectrum of which no longer appears to be currently adapted to the empirical treatment of prosthetic infection [67]. Vancomycin poses the problem of its nephrotoxic potential [70]. Daptomycin has a profile that is adapted to all of these prerequisites, but it does not have an approval for this type of use [71].

3.1.3.3. Gram-negative bacilli

Bacterial ecology is highly variable from one health facility to another, and as such it is difficult to recommend a standardised anti-Gram-negative bacilli empirical antibiotic therapy. The empirical prescription of amoxicillin/clavulanic acid appears inadequate because of the increasing prevalence of resistant *Escherichia coli*, exceeding one-third of strains [72]. The combinations piperacillin/tazobactam and ticarcillin/clavulanic acid have an advantage over cephalosporins because they cover obligate anaerobes, including *Bacteroides fragilis*.

The increase in carbapenemase-producing bacteria in human pathology restricts the use of carbapenems to severe infections and/or when the patient has multidrug-resistant bacteria [73].

Aminoglycosides may be useful to intensify bactericidal activity and to rapidly reduce the bacterial inoculum, but they expose patients to the risk of nephrotoxicity, particularly patients with chronic renal failure or cirrhosis. The impact of their use on mortality varies: one study found no benefit of aminoglycosides on mortality rates

[41], whereas a separate study found that aminoglycosides might reduce mortality when used for patients in intensive care (59% vs. 27%; $P = 0.07$ in multivariate analysis) [42].

3.2. Recommendations

It is recommended that the use of empirical antibiotic therapy should be limited to suspected or known cases of PVGI for which it does not seem reasonable to wait for surgical microbiological sample results. Such situations include severe sepsis, septic shock, and instances in which the clinical and/or radiological signs indicate a mechanical complication of infectious origin, such as an aneurysmal rupture or anastomotic disunion (C-III). Two different sets of blood cultures should systematically be performed prior to empirical antibiotherapy.

Adaptation is necessary after receiving the microbiological results from blood cultures or surgical samples. Such 'de-escalation' should be performed as quickly as possible to limit the selection pressure for resistant strains that is induced by this broad-spectrum antibiotic therapy (B-III).

Table 2 presents proposals for empirical antibiotic therapy depending on the clinical situation (C-III).

The potential severity of PVGIs, their frequent association with bacteraemia, and the need for sufficient concentrations at the site of the infected material

interface/periprosthetic tissue are good arguments for parenteral administration and the use of high dosages (C-III).

4. Documented antibiotic therapy

The following proposals reflect the prerequisites outlined above (good diffusion in the biofilm, activity against slowly metabolising strains, high tolerance, need for bactericidal treatment) and result from an analysis of the PVGI literature and the most recent recommendations for the treatment of prosthetic valve endocarditis [34,74–76]. Although PVGIs cannot be entirely likened to infective endocarditis (IE), these two types of infection have many points in common, including infection of endovascular material with production of biofilm, patients with multiple co-morbidities, frequently impaired renal function, and similarity of causative micro-organisms, with the exception of Enterobacteriaceae and obligate anaerobic bacteria that are often encountered in cases of PVGI but are rare in IE.

Blood cultures and/or periprosthetic collection punctures can serve to document the infection prior to surgery. The following recommendations therefore distinguish two situations: pre-operative and post-operative antibiotic therapy. For the post-operative part, two situations are distinguished: optimal management (excision of the entire infected prosthesis and the surrounding infected tissue); and suboptimal surgery (all or part of the prosthesis left in place). In the absence of pre-operative documentation, the antibiotic therapy recommendations are outlined in Section 3.

There are no data regarding the impact of the surgical procedure performed on the antibiotherapy. It is not known whether the type of biomaterial used for the vascular reconstruction after infected graft removal (autogenous venous graft, cryopreserved arterial allograft, prosthetic graft) or the surgical procedure performed (extra-anatomical or in situ reconstruction) influence the choice or duration of antibiotic treatment. It is therefore recommended to apply the same medical treatment for all of the different surgical techniques (C-III).

It is also not known whether the anatomical site or the type of infected material impact the choice of antibiotherapy. In the literature, peripheral lower limb VGI and aortic VGI are often individualised but only for the surgical procedure and not for the medical treatment. Prosthetic dialysis arteriovenous graft infections have also been specifically studied but only in three studies [77–79], and data dealing with antibiotics are too scarce to propose specific medical treatment for these infections. Thus, it is recommended to adopt the same medical treatment for all the different types of PVGIs (C-III).

The dosages and modes of administration of the various compounds mentioned are provided in Table 3. Generally (B-III):

- In the event of reliable pre-operative documentation (deep sampling performed through healthy dermal route or positive blood culture), antibiotic therapy should target only the pathogen or pathogens found.
- Post-operative re-evaluation of this antibiotic therapy should be carried out in light of the intra-operative sampling results.

- Surgical treatment should be performed as quickly as possible because of the extreme severity of PVGIs in order to facilitate the efficacy of the anti-infective therapy. This is particularly important in cases of micro-organisms that are difficult to treat, such as multiresistant bacteria, enterococci, *P. aeruginosa* and yeasts.

4.1. Staphylococcal infections

4.1.1. Rationale

Although not new [80], data regarding the efficacy of meticillin derivatives are still valid [81] and the use of these derivatives remains highly recommended as the first-line treatment for severe meticillin-sensitive *S. aureus* infections [34,75,76,82]. In the case of penicillin allergy without allergy to cephalosporins, the choice will be between cefazolin, vancomycin and daptomycin. In the case of allergy to all β -lactams, the choice will be between vancomycin and daptomycin [34,81,83–90].

Treatment of MRSA infections is difficult. Vancomycin is established by usage as the compound of choice, although failures are reported, particularly in cases of high vancomycin MICs (≥ 1.5 mg/L) [91,92].

Given that PVGIs are severe infections on foreign materials, addition of an aminoglycoside, preferably gentamicin, is justified [59,93–95].

Addition of rifampicin is attractive because of its large diffusion capacity, anti-adhesion potency and preserved bactericidal activity despite the presence of a

biofilm [59,60,96]. Its use is also correlated with a better prognosis in osteoarticular staphylococcal infections [97]. Its prescription as monotherapy is strongly discouraged, as is its use in bacteraemic patients [98], owing to the rapid emergence of a resistant strain of bacteria. There are no data regarding the use of rifampicin in PVGIs, but the pharmacological, clinical and experimental data argue in favour of its use. Therefore, in the treatment of staphylococcal PVGIs, it is advisable to add rifampicin to the treatment after vascular surgery and certainty of negative blood cultures.

Daptomycin exhibits interesting bactericidal activity within the biofilm [58,99]. It is approved for bacteraemia and right-sided endocarditis caused by *S. aureus* at a dose of 6 mg/kg/day in a single injection [100]. However, there appears to be a possibility of decreased staphylococci susceptibility during treatment [101] and a greater number of microbiological failures compared with comparators [100], suggesting that the dose of 6 mg/kg/day may be insufficient. Some authors have also shown that higher doses (8–12 mg/kg/day) do not pose any particular tolerance problems [102,103], although it is not known whether this increase in dosage changes the prognosis of infections. However, no data are available regarding the use of daptomycin in the treatment of PVGIs, and the use of this compound as first-line therapy should be subject to a multidisciplinary approach when the staphylococcal strain is sensitive to meticillin and vancomycin (MICs < 1.5 mg/L). In staphylococcal infections caused by strains with vancomycin MICs \geq 1.5 mg/L, the use of daptomycin is advised, at high doses, in combination with gentamicin for the first 3 days of treatment, followed by rifampicin. Daptomycin MICs for the isolated

strain should be documented. It has indeed been shown that sensitivity to daptomycin may decrease when the vancomycin MIC is elevated [104,105].

No scientifically valid data provide a basis for preferring one compound to another for PVGIs caused by glycopeptide-resistant staphylococci. However, daptomycin is the compound for which data related to use on foreign material [106] and IE [100] are the most documented. To improve efficacy and reduce the risk of emergence of strains with reduced susceptibility to daptomycin during treatment, it should be combined with another antibiotic, preferably gentamicin [107] or rifampicin [108].

For other antistaphylococcal agents, no data are available for this type of infection and their use should be considered only on a case-by-case basis, in combination, in the absence of an alternative and following a multidisciplinary opinion.

4.1.2. Recommendations

Therapeutic proposals for PVGIs caused by staphylococci (*S. aureus* or CoNS) are presented in Tables 4 and 5.

4.2. Streptococcal infections

4.2.1. Rationale

There is no study specific to the treatment of streptococcal PVGIs. Therefore, the following recommendations stem from extrapolations from comparable clinical

situations for which reliable data are available. Amoxicillin remains the antibiotic of choice for streptococcal infections [34,75,82,109–111].

The use of aminoglycosides for treating severe streptococcal infections is currently under debate because of their potential toxicity [112]. Analysis of the literature does not support any conclusion regarding their usefulness [113–116]. Their use in the first days of treatment to reduce bacterial inocula appears to be justified.

Post-operatively, this benefit is more questionable: the bacterial inoculum is reduced by surgery, and the remaining bacteria are located in the periphery of the prosthesis, in an extravascular position, an area in which the diffusion of aminoglycosides is very limited. If vancomycin is used, co-administration of gentamicin is not recommended because of the low level of evidence regarding its use in this context and the risk of renal toxicity associated with this combination. When used, gentamicin is given in a single daily dose [93].

The effectiveness of other antibiotics with antistreptococcal activity in PVGI treatment has not yet been established.

4.2.2. Recommendations

4.2.2.1. Pre-operative treatment

Determination of MICs of amoxicillin, cefotaxime and/or ceftriaxone, or even vancomycin, should be obtained, particularly in cases of *viridans* streptococci infection (B-III). Amoxicillin is the recommended treatment for streptococcal PVGIs

that are sensitive to this compound, with dosages ranging from 100 mg/kg/day (streptococci for which the amoxicillin MIC is <0.125 mg/L) to 200 mg/kg/day (MIC ≥ 0.125 mg/L) divided into four to six injections (B-III). Gentamicin can be added, for a maximum period of 3 days, at a dose of 3–8 mg/kg/day (C-III).

Vancomycin is the antibiotic of choice (B-III) when susceptibility to all β -lactam antibiotics is decreased or in the case of allergy to all members of this therapeutic class. Determination of the vancomycin MIC is therefore imperative. Combination with gentamicin is not systematic; it is only considered in the event of signs of severe sepsis or septic shock, and its use is then restricted to ≤ 3 days (C-III).

4.2.2.2. Post-operative treatment

4.2.2.2.1. For optimal surgical treatment

Post-operative treatment is the same as that recommended for pre-operative treatment (B-III). The duration of treatment is 6 weeks post-operatively, parenterally (C-III).

4.2.2.2.2. For suboptimal surgical treatment

Antibiotic treatment is the same as in the previous situation for 6 weeks post-operatively (B-III). Subsequently, switching to oral amoxicillin can be considered (C-III).

4.3. Enterococcal infections

4.3.1. Rationale

In the absence of high-level resistance to gentamicin, the combination of amoxicillin + gentamicin is synergistic and bactericidal [117,118]. Extrapolation of data regarding endocarditis would serve to restrict the duration of use of gentamicin [119]. Post-operatively, due to the decrease of inoculum, treatment with aminoglycoside is temporally shortened.

Experimental data have shown that the ampicillin + ceftriaxone combination may act synergistically when used in the treatment of experimental endocarditis caused by *Enterococcus faecalis* [120,121]. Human clinical data also appear to confirm this [122,123]. This combination could be an option in the case of significant toxicity of aminoglycosides or pre-existing renal insufficiency.

For PVGIs caused by vancomycin-resistant enterococci, there is not yet enough solid evidence to recommend one compound over another [124]. Linezolid has sometimes been used [125,126], most often in combination with other compounds, but its prolonged use is difficult because of its neurological and haematological toxicity and potential risk of relapse [127,128]. Some experimental studies [129] or clinical cases [130] also reported the efficacy of daptomycin in this indication, but the emergence of resistant strains [131,132] makes its use problematic. However, some in vitro data appear to indicate a real synergy between daptomycin and rifampicin or ampicillin against enterococci [133,134]. Monitoring of a cohort of 159 patients (90% bacteraemic) treated with daptomycin for enterococcal infection, 115 of whom were

resistant to vancomycin, showed a cure rate of 44% [135]. It is not possible to be categorical regarding the choice of the compound to be used in glycopeptide-resistant PVGIs caused by enterococci [136]. This choice must be made after multidisciplinary discussion.

4.3.2. Recommendations

4.3.2.1. Pre-operative treatment

Amoxicillin is the recommended treatment for PVGIs caused by susceptible enterococci. The dose is 200 mg/kg/day divided into four to six injections (B-III). Gentamicin is used, in a single daily dose, for 7 days at a dose of 3–8 mg/kg/day if surgery is not performed before treatment (B-III).

In the case of allergy or resistance to amoxicillin, teicoplanin or vancomycin alone is recommended (B-III). In the case of resistance to glycopeptides, the susceptibility of enterococcus to daptomycin and linezolid must be studied. The choice will be made following a multidisciplinary opinion (C-III).

4.3.2.2. Post-operative treatment

4.3.2.2.1. For optimal surgical treatment

Post-operative treatment is the same as that recommended for pre-operative treatment regarding amoxicillin or glycopeptides (B-III). Gentamicin is continued only for a maximum of 3 days (C-III). The duration of treatment is 6 weeks post-operatively, parenterally, at the same dosage (C-III).

4.3.2.2.2. For suboptimal surgical treatment

Antibiotic treatment is the same as in the previous situation for 6 weeks post-operatively (C-III). Subsequently, oral amoxicillin relay, for an extended period, can be considered (C-III).

4.4. Enterobacteriaceae infections

4.4.1. Rationale

The benefit of combination therapy in infections caused by enterobacteria is controversial [137]. The synergistic effect and prevention of resistance has not been demonstrated by clinical studies [137–144]. However, the severity of PVGIs and the risk of severe systemic impact justify the initial combination of an aminoglycoside with a β -lactam for a short period of time [93].

4.4.2. Recommendations

Therapeutic proposals for PVGIs caused by Enterobacteriaceae are presented in Table 6.

4.5. *Pseudomonas* infections

4.5.1. *Rationale*

On a compromised terrain and high inoculum, the slightest susceptibility to antibiotics and resistance make the treatment of PVGIs caused by *Pseudomonas* difficult. The benefit of combination therapy that has not been shown by discordant and heterogeneous clinical studies [145–148] remains established by usage prior to surgery and post-operatively.

4.5.2. *Recommendations*

4.5.2.1. Pre-operative treatment

Treatment is based on a β -lactam, and the choice is made according to the results of antibiotic susceptibility testing among ticarcillin, ceftazidime, piperacillin/tazobactam and a carbapenem (excluding ertapenem) (B-III). An aminoglycoside (amikacin or tobramycin) is combined with it for 3 days (C-III). The aminoglycoside is replaced by fosfomycin beyond these 3 days if the surgery has not yet been performed (C-III). Fluoroquinolones should be reserved for post-operative oral relay (B-III).

4.5.2.2. Post-operative treatment

4.5.2.2.1. *For optimal surgical treatment*

Combination therapy is continued, with the β -lactam selected pre-operatively being used in conjunction with ciprofloxacin or fosfomycin, depending on antibiotic susceptibility testing (C-III). This combination therapy is continued for ≥ 3 weeks, for a total of 6 weeks post-operatively (C-III).

4.5.2.2.2. For suboptimal surgical treatment

Multidisciplinary opinion (C-III).

4.6. Obligate anaerobic bacterial infections

4.6.1. Rationale

Metronidazole, which is consistently active against obligate anaerobes, particularly *B. fragilis*, is the compound of choice. Its absorption and exceptional diffusion allow its use as oral monotherapy [149]. *Propionibacterium acnes*, which is naturally resistant to imidazole, is susceptible to amoxicillin. Surgery is essential because relapse when the prosthetic material is left in place is virtually systematic [150]. Clindamycin, in addition to the risk of *Clostridium difficile* colitis, does not have a satisfactory anti-anaerobic spectrum, particularly against *B. fragilis*, which limits its empirical prescription in cases of PVGI [149].

4.6.2. Recommendations

4.6.2.1. Pre-operative treatment

Metronidazole is the first-line treatment for obligate anaerobic infections apart from *P. acnes*. It may be administered orally or intravenously (B-III). PVGIs caused by *P. acnes* are treated with intravenous amoxicillin (B-III). Monotherapy is sufficient (B-III).

4.6.2.2. Post-operative treatment

4.6.2.2.1. For optimal surgical treatment

The treatment is the same as pre-operative management (B-III). The total duration of treatment is 6 weeks (C-III).

4.6.2.2.2. For suboptimal surgical treatment

Suppressive oral amoxicillin treatment may be proposed for PVGIs caused by *P. acnes* and following a multidisciplinary opinion (C-III). For other obligate anaerobes such as *B. fragilis*, the possibility of suppressive treatment should be evaluated after multidisciplinary consultation (C-III).

4.7. Polymicrobial infections

Susceptibility testing should be performed for each of the isolated bacteria. Several compounds may sometimes be necessary to cover all of the bacteria considered pathogenic. A multidisciplinary opinion is necessary (B-III). The presence of obligate anaerobes does not require metronidazole if one of the combination antibiotics is already active on these bacteria (B-III).

5. Duration of treatment of bacterial prosthetic vascular graft infections and methods of administration

5.1. Rationale

Analysis of treatment duration from different studies is difficult to interpret because of: (i) the non-comparative nature of these studies; (ii) studies that do not include standardised durations or feature highly variable durations; and (iii) the use of a wide variety of compounds. In all of these studies, patients underwent surgery. The durations of antibiotic therapy are variable, ranging from 2 weeks after surgery [15,31] to 6 months [30], or even lifelong [22]. Many studies report durations of 6 weeks post-operatively [5,7,9,11–14,25,27,28,35,37] without the risk of relapse appearing greater than that encountered when the treatment period is longer. This 6-week duration is the same as that proposed in the treatment of prosthetic valve endocarditis [34,82].

5.2. Recommendations

The total duration of post-operative antibiotic therapy proposed for PVGIs is 6 weeks for optimal surgical treatment (C-III). It should be administered parenterally. When using compounds with good bioavailability (rifampicin, fluoroquinolones), oral administration is possible.

6. Methods of administration of anti-infective agents

These methods are presented for normal renal and hepatic function in Table 3. In patients with renal or hepatic impairment, an adjustment may be required.

7. Suppressive antibiotic therapy

7.1. Rationale

In the absence of surgery, or in cases of suboptimal surgery, suppressive antibiotic therapy is administered. Its aim is to inhibit bacterial growth around the prosthesis, or what is left of it. By analogy with infections on osteoarticular material [151], it is assumed that in the stationary growth phase, bacteria remain on the material that cannot be eliminated by intensive antibiotic therapy. Even with very high dosage and very long duration, antibiotherapy alone is not supposed to cure PVGIs [152]. For instance, a recent study dealing with aortic endograft infection demonstrated that all of the patients who did not undergo endograft removal died during follow-up [49].

Suppressive treatment is only conceivable in the case of documented infection. In cases of periprosthetic abscess, radiological drainage should be performed if possible to reduce the bacterial inoculum as much as possible. No formal studies currently serve to validate this approach.

7.2. Recommendations

Suppressive antibiotic therapy is administered in the absence of surgery or in the case of suboptimal surgery (C-III). This antibiotic therapy will follow a 6-week period

of intensive antibiotic therapy (B-III). It should therefore be easy to administer (orally), well tolerated and feasible as monotherapy. The choice of compound used should result from a multidisciplinary approach (B-III).

8. Specific case of fungal infection

8.1. Rationale

This essentially relates to yeast infections, such as *Candida*, in the context of bacterial co-infections. The therapeutic choice is made between amphotericin B derivatives (liposomal or lipid complex), azoles (mainly fluconazole) and echinocandins. The theoretical prerequisites are fungicidal treatment with activity preserved in the biofilm, anti-adhesion effect, proper dissemination to the infectious site and good tolerance. For this last reason, amphotericin B, which is nephrotoxic, is not recommended because of the frail nature of the patients.

Echinocandins have a good safety profile (including renal), in vitro fungicidal activity against yeasts, and good action in the case of existence of biofilm [153]. Their use is recommended by several scientific societies as a first-line treatment of moderate-to-severe infections [154]. One key disadvantage of using echinocandins is that they are available only for parenteral administration. There is a restriction on the use of micafungin (risk of liver tumours observed in a mouse model).

8.2. Recommendations

Isolation of the fungus and antifungal susceptibility testing are essential. An echinocandin (caspofungin, micafungin or anidulafungin, if available) is used as a first-line treatment for 10 days post-operatively and/or 10 days after the last positive blood culture for *Candida* (C-III). If the strain is susceptible, if blood cultures are negative for ≥ 10 days and if the clinical situation has stabilised, an oral relay treatment with fluconazole may be taken on Day 10: loading dose of 800 mg on the first day followed by a one-time dose of 400–800 mg/day (B-III). The duration of treatment is ≥ 6 weeks post-operatively and 3 months in cases involving a periprosthetic abscess (C-III).

9. Conclusions

PVGIs are infections burdened with heavy rates of morbidity and mortality, the frequency of which are rising because of surgical advances and endovascular techniques that make it possible to implant an increasing number of prostheses. No data currently provide solid evidence regarding the antimicrobial therapy to be administered to patients suffering from PGVIs. A comprehensive literature review was therefore conducted. We hope that the proposals resulting from this analysis will help practitioners with regard to the care of these patients. It is increasingly vital to validate these proposals by means of further research investigating this issue, and we hope that the results of such studies will soon be available.

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Table 1

Levels of evidence and grades of recommendations used

| Level of evidence provided by the literature | Grade of recommendations |
|--|---------------------------------|
| Level I | A |
| High-quality randomised controlled trials | Established scientific evidence |
| Meta-analysis of randomised controlled trials | |
| Decision analysis based on well conducted studies | |
| Level II | B |
| Low-quality randomised controlled trials | Scientific presumption |
| Non-randomised, well conducted comparative studies | |
| Cohort studies | |
| Level III | C |
| Case-control studies | Low level of evidence |
| Level IV | |
| Comparative studies with significant biases | |
| Retrospective studies | |
| Case series | |

Table 2

Empirical antibiotic therapy for prosthetic vascular graft infections (PVGIs) depending on the clinical situation (C-III)

| Clinical situation | In the absence of allergy to β -lactams | In the case of allergy to penicillin |
|---|---|--|
| PVGI with sepsis without signs of severity or known colonisation, no history of MDR bacterial infection | Piperacillin/tazobactam + vancomycin or daptomycin ^a \pm gentamicin | Cefotaxime or ceftriaxone or cefepime or aztreonam + metronidazole + vancomycin or daptomycin ^a \pm gentamicin |
| PVGI with sepsis, signs of severe sepsis and/or known colonisation or previous infection with ESBL-GNB ^b | Imipenem or meropenem or doripenem + vancomycin or daptomycin ^a \pm gentamicin | Fosfomycin + metronidazole + vancomycin or daptomycin ^a \pm gentamicin |
| MDR, multidrug-resistant; ESBL-GNB, extended-spectrum β -lactamase-producing Gram-negative bacillus. | | |

^a No approval for this indication.

^b Resistant to third- or fourth-generation cephalosporins on antibiotic susceptibility testing.

Table 3

Dosage, route and rate of administration of anti-infectives in prosthetic vascular graft infections

| Compound | Dosage | Route and rate of administration |
|-----------------------------|---|---|
| Amikacin | 15–30 mg/kg/day | One i.v. infusion over 30 min |
| Amoxicillin | 100–200 mg/kg/day | Six i.v. infusions over 30 min or i.v. via infusion pump |
| Amoxicillin/clavulanic acid | 100–200 mg/kg/day of amoxicillin | Six i.v. infusions over 30 min (2 g vials) |
| Caspofungin | 70 mg the first day and then 50 mg/day (weight <80 kg) or 70 mg/day (weight ≥80 kg) | One i.v. infusion over 1 h |
| Cefazolin | 60–80 mg/kg/day | Six i.v. infusions over 30 min or i.v. via infusion pump ^a |
| Cefotaxime | 150 mg/kg/day | Six i.v. infusions over 30 min or i.v. via infusion pump ^a |
| Ceftazidime | 100 mg/kg/day | Four i.v. infusions over 30 min or i.v. via infusion pump ^a |
| Ceftriaxone | 50 mg/kg/day | One to two i.v. infusions over 30 min |
| Ciprofloxacin | 1500–2000 mg/day (orally) or 800–1200 mg/day (i.v.) | Two to three oral doses ^b or two to three i.v. infusions over 30 min ^b |

| | | |
|--------------------------|--|---|
| Cloxacillin or oxacillin | 200 mg/kg/day | Six i.v. infusions over 30 min or i.v. via infusion pump on three syringes over 8 h ^a |
| Daptomycin | 8–10 mg/kg/day | One i.v. infusion over 2–30 min |
| Doripenem | 3 g/day | Three i.v. infusions over 4 h or i.v. via infusion pump (500 mg in 50 mL to 12 mL/h) |
| Fluconazole | 800 mg on the first day and 400–800 mg/day | One oral dose or one i.v. infusion over 2 h ^c |
| Fosfomycin | 150–200 mg/kg/day | Three to four i.v. infusions over 3–4 h |
| Gentamicin | 3–8 mg/kg/day | One i.v. infusion over 30 min |
| Imipenem | 3 g/day | Three i.v. injections over 30 min |
| Levofloxacin | 500–1000 mg/day | One oral dose or one i.v. infusion over 30 min ^b |
| Meropenem | 3–6 g/day | Three i.v. infusions over 30 min |
| Metronidazole | 1500 mg/day | Three oral doses or three i.v. infusions over 30 min ^c |
| Micafungin | 100 mg/day | One i.v. infusion over 1 h |

| | | |
|--------------------------|---|---|
| Ofloxacin | 400–600 mg/day | Two oral doses or two i.v. infusions over 30 min ^b |
| Piperacillin/tazobactam | 150–200 mg/kg/day of piperacillin | Three infusions over 4 h |
| Rifampicin | 10–20 mg/kg/day | Two oral doses (fasting) or two i.v. infusions over 30 min ^c |
| Teicoplanin ^d | 8–12 mg/kg/12 h for 3 days and then 8–12 mg/kg/day | Slow i.v., i.m. or subcutaneous |
| Ticarcillin | 250 mg/kg/day | Three i.v. infusions over 30 min or i.v. via infusion pump ^a |
| Vancomycin ^d | 40–60 mg/kg/day | i.v. via infusion pump ^a |

i.v., intravenous; i.m., intramuscular.

^a Begin with a loading dose equal to one-quarter of the total daily dose, to be administered over 30 min via i.v. infusion, except for vancomycin for which the duration of administration of the loading dose is longer: 15 mg/kg loading dose to be infused over 1 h (1 g) or 1 h 30 min (1.5 g).

^b The highest dosages of fluoroquinolones are to be considered when combined with rifampicin owing to the enzyme induction properties of the latter.

^c Preference should be given to oral administration.

^d Glycopeptide dosage: this will be done after 72 h for vancomycin and after the sixth infusion for teicoplanin (just before the infusion) and then once a week for the entire duration of the treatment.

Table 4

Antibiotic therapy for prosthetic vascular graft infections caused by meticillin-sensitive *Staphylococcus* sp.

| | In the absence of allergy to β - lactams | In the case of allergy to penicillin | In the case of contraindication to β -lactams |
|----------------------------|---|---|---|
| Pre-operative treatment | Cloxacillin or oxacillin (B-III) + gentamicin ^a 3 days (B-III) | Cefazolin or vancomycin or daptomycin (B- III) + gentamicin ^a 3 days (B-III) | Vancomycin or daptomycin (B- III) + gentamicin ^a 3 days (B-III) |

| | | | | |
|--------------------------|---------|--|---|--|
| Post-operative treatment | Optimal | Cloxacillin or oxacillin (B-III) + gentamicin ^a 3 days (C-III) and then addition of rifampicin ^b in place of gentamicin (B-III) relay with oral rifampicin + fluoroquinolone at Day 15 post-operatively ^c (C-III) Duration of treatment, 6 weeks post-operatively (C-III) | Cefazolin or vancomycin or daptomycin (B-III) + gentamicin ^a 3 days (C-III) and then addition of rifampicin ^b in place of gentamicin (B-III) relay with oral rifampicin + fluoroquinolone at Day 15 post-operatively ^c (C-III) Duration of treatment, 6 weeks post-operatively (C-III) | Vancomycin or daptomycin (B-III) + gentamicin ^a 3 days (C-III) and then addition of rifampicin ^b in place of gentamicin (B-III) relay with oral rifampicin + fluoroquinolone at Day 15 post-operatively ^c (C-III) Duration of treatment, 6 weeks post-operatively (C-III) |
|--------------------------|---------|--|---|--|

| | | | |
|------------|---|---|--|
| Suboptimal | Cloxacillin or oxacillin (B-III) + gentamicin 3 days (C-III) and then addition of rifampicin ^b in place of gentamicin (B-III) for 6 weeks post- operatively (C- III) and then suppressive treatment ^d (C- III) | Cefazolin or vancomycin or daptomycin (B- III) + gentamicin 3 days (C-III) and then addition of rifampicin ^b in place of gentamicin (B-III) for 6 weeks post- operatively (C- III) and then suppressive treatment ^d (C-III) | Vancomycin or daptomycin + gentamicin 3 days and then addition of rifampicin ^b in place of gentamicin (B-III) for 6 weeks post- operatively (C-III) and then suppressive treatment ^d (C-III) |
|------------|---|---|--|

^a Dosage of 3–8 mg/kg/day in a single daily dose. In patients with severe infection with the risk of increased volume of distribution (severe sepsis or even septic shock, mechanical ventilation, presence of oedema, etc.), preference should be given to higher doses (5–8 mg/kg/day). The rate of administration and dosages are to be adapted to residual concentrations.

^b After ascertaining that blood cultures are negative.

^c Only in the case of good clinical evolution, if susceptible to fluoroquinolones and in the absence of post-operative bacteraemia. No other oral relay is recommended (C-III).

^d To be determined based on susceptibility testing and following a multidisciplinary opinion.

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Table 5

Antibiotic therapy for prosthetic vascular graft infections caused by methicillin-resistant *Staphylococcus* sp.

| | | Vancomycin MIC < 1.5 mg/L | Vancomycin MIC ≥ 1.5 mg/L |
|--------------------------|---------|--|--|
| Pre-operative treatment | | Vancomycin ^a (B-III) or daptomycin (C-III) + gentamicin 3 days (B-III) | Daptomycin (B-III) + gentamicin 3 days (C-III) |
| Post-operative treatment | Optimal | Vancomycin ^a (B-III) or daptomycin (C-III) + gentamicin 3 days (C-III) and then addition of rifampicin ^b in place of gentamicin (B-III) relay with oral rifampicin + fluoroquinolone at Day 15 post-operatively ^c (C-III) Duration of treatment, 6 weeks post-operatively (C-III) | Daptomycin (B-III) + gentamicin 3 days (C-III) and then addition of rifampicin ^b in place of gentamicin (B-III) relay with oral rifampicin + fluoroquinolone at Day 15 post-operatively ^c (C-III) Duration of treatment, 6 weeks post-operatively (C-III) |

| | | |
|------------|--|---|
| Suboptimal | Vancomycin (B-III) or daptomycin (C-III) + gentamicin 3 days (C-III) and then addition of rifampicin in place of gentamicin (B-III) for 6 weeks post-operatively (C-III) and then suppressive treatment ^d (C-III) | Daptomycin (B-III) + gentamicin 3 days (C-III) and then addition of rifampicin in place of gentamicin (B-III) for 6 weeks post-operatively (C-III) and then suppressive treatment ^d (C-III) |
|------------|--|---|

MIC, minimum inhibitory concentration.

^a Equilibrium concentrations of vancomycin, 20–30 mg/L. Teicoplanin can be considered, as a relay, after ascertaining the susceptibility of the bacterial strain and if the clinical condition has stabilised (C-III).

^b After ascertaining that blood cultures are negative.

^c Only in the case of good clinical evolution, if susceptible to fluoroquinolones and in the absence of post-operative bacteraemia.

^d To be determined based on susceptibility testing and after multidisciplinary opinion.

Table 6

Antibiotic treatment of prosthetic vascular graft infections caused by
Enterobacteriaceae

| | | In the absence of allergy to β -lactams | In the case of allergy to penicillin |
|-----------------------------|------------|---|--|
| Pre-operative treatment | | Ceftriaxone or cefotaxime ^a (B-III) + gentamicin 3 days ^b (C-III) | Aztreonam (C-III) + gentamicin 3 days (C-III) |
| Post-operative treatment | Optimal | Ceftriaxone or cefotaxime ^a (B-III) and then relay with fluoroquinolones ^c (C-III) | Aztreonam (C-III) and then relay with fluoroquinolones ^c (C-III) |
| | | Duration of treatment, 6 weeks post-operatively (C-III) | Duration of treatment, 6 weeks post-operatively (C-III) |
| | Suboptimal | Ceftriaxone or cefotaxime ^a (B-III) and then relay with fluoroquinolones ^c (C-III) for 6 weeks post- operatively (C-III) | Aztreonam (C-III) and then relay with fluoroquinolones ^c for 6 weeks post-operatively (C-III) |
| | | and then suppressive treatment ^d (C-III) | and then suppressive treatment ^d |

^a Use of another narrower-spectrum β -lactam is possible based on the susceptibility testing data and following a specialist opinion.

^b The dose of gentamicin is between 5 mg/kg/day and 8 mg/kg/day. Higher doses are preferable in the case of septic shock (B-III).

^c The relay is done 15 days post-operatively in the case of good evolution. It can also be done earlier in the case of good evolution when aztreonam is used. If bacteria are resistant to fluoroquinolones and nalidixic acid, continue with β -lactam antibiotics for 6 weeks post-operatively (B-III).

^d To be determined based on susceptibility testing and following a multidisciplinary opinion.

a.